What is claimed:

1. A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi) and wherein the sense strand or antisense strand is modified by the substitution of at least one internal nucleotide with a modified nucleotide, such that *in vivo* stability is enhanced as compared to a corresponding unmodified siRNA.

2. A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi) and wherein the sense strand or antisense strand is modified by the substitution of at least one internal nucleotide with a modified nucleotide, such that the target efficiency is enhanced compared to a corresponding unmodified siRNA.

3. The siRNA of claim 1 or 2 which is sufficiently complementary to a target mRNA, said target mRNA specifying the amino acid sequence of a cellular protein.

4. The siRNA of claim 1 or 2 which is sufficiently complementary to a target mRNA, said target mRNA specifying the amino acid sequence of a viral protein.

5. The siRNA of any one of claims 1-4, wherein the modified nucleotide is a sugar-modified nucleotide.

6. The siRNA of any one of claims 1-4, wherein the modified nucleotide is a nucleobase-modified nucleotide.

7. The siRNA of any one of claims 1-4, wherein the modified nucleotide is a 2'-deoxy ribonucleotide and is present within the sense strand.

8. The siRNA of any one of claims 1-4, wherein the modified nucleotide is a 2'-fluoro modified ribonucleotide.

9. The siRNA of any one of claims 1-4, wherein the modified nucleotide is selected from the group consisting of a 2'-fluoro, 2'-amino and 2'-thio modified ribonucleotide.

10. The siRNA of any one of claims 1-4, wherein the modified nucleotides are a 2'-fluoro modified ribonucleotide and a 2'-deoxy ribonucleotide.

11. The siRNA of claim 10, wherein the 2'-fluoro modified ribonucleotide is 2'-fluoro uridine or 2'-fluoro cytidine.

12. The siRNA of claim 10, wherein the 2'-deoxy ribonucleotide is 2'-deoxy adenosine or 2'-deoxy guanosine.

13. The siRNA of any one of claims 10-12, wherein the 2'-deoxy ribonucleotides are in the antisense strand.

14. The siRNA of claim 13, wherein the 2'-deoxy ribonucleotides are upstream of the cleavage site referencing the antisense strand.

15. The siRNA of claim 13, wherein the 2'-deoxy ribonucleotides are downstream of the cleavage site referencing the antisense strand.

16. The siRNA of any one of claims 10-15, wherein the 2'-fluoro ribonucleotides are in the sense and antisense strands.

17. The siRNA of any one of claims 10-15, wherein the 2'-fluoro ribonucleotides are every uridine and cytidine.

18. The siRNA of claim 5, wherein the modified nucleotide is selected from the group consisting of 2'-fluoro-cytidine, 2'-fluoro-uridine, 2'-fluoro-adenosine, 2'-fluoro-guanosine, 2'-amino-cytidine, 2'-amino-uridine, 2'-amino-adenosine, 2'-amino-guanosine and 2'-amino-butyryl-pyrene-uridine.

19. The siRNA of claim 6, wherein the modified nucleotide is selected from the group consisting of 5-bromo-uridine, 5-iodo-uridine, 5-methyl-cytidine, ribo-thymidine, 2-aminopurine, 5-fluoro-cytidine, and 5-fluoro-uridine, 2,6-diaminopurine, 4-thio-uridine; and 5-amino-allyl-uridine.

20. The siRNA of any one of claims 1-4, wherein the modified nucleotide is a backbone-modified nucleotide

21. The modified siRNA of claim 20, wherein the backbone-modified nucleotide contains a phosphorothioate group.

22. The modified siRNA of claim 20, wherein the backbone-modified nucleotide contains a phosphorothioate group and is present within the sense and antisense strands.

23. The siRNA of any one of the preceeding claims, wherein the sense strand is crosslinked to the antisense strand

24. The siRNA of claim 23, wherein the crosslink is present dowstream of the cleavage site referencing the antisense strand.

25. The siRNA of claim 23, wherein the crosslink is present at the 5' end of the sense strand.

26. The siRNA of any one of claims 1-4, wherein the antisense strand and target mRNA sequences are 100% complementary.

27. The siRNA of any one of claims 1-4, wherein the antisense strand and target mRNA sequences comprise at least one mismatch.

28. The siRNA of claim 27, wherein the mismatch is downstream of the cleavage site referencing the antisense strand.

29. The siRNA of claim 27, wherein the mismatch is present within 1-6 nucleotides from the 3' end of the antisense strand.

30. The siRNA of any one of the preceeding claims, wherein a 3' OH terminus of the sense strand or antisense strand is modified.

31. The siRNA of any one of claims 1-4, wherein the modified nucelotide does not effect the ability of the antisense strand to adopt A-form helix conformation when base-pairing with the target mRNA sequence.

32. The siRNA of any one of claims 1-4, wherein the modified nucelotide does not effect the ability of the antisense strand to adopt A-form helix conformation comprising a normal major groove when base-pairing with the target mRNA sequence.

33. The siRNA of any one of claims 1-4, which is between about 10 and 50 residues in length.

34. The siRNA of any one of claims 1-4, which is between about 15 and 45 residues in length.

35. The siRNA of any one of claims 1-4, which is between about 20 and 40 residues in length.

36. The siRNA of any one of claims 1-4, which is between about 18 and 25 residues in length.

37. The siRNA of any one of claims 1-4, which is chemically synthesized.

38. A transgene that encodes the siRNA of any one of claims 1-4.

39. A composition comprising the siRNA molecule of any one of claims 1-37 and a pharmaceutically acceptable carrier.

40. A method of activating target-specific RNA interference (RNAi) in a cell comprising introducing into said cell the siRNA of any one of the preceding claims, said siRNA being introduced in an amount sufficient for degradation of target mRNA to occur, thereby activating target-specific RNAi in the cell.

41. The method of claim 40, wherein the siRNA is introduced into the cell by contacting the cell with the siRNA.

42. The method of claim 41, wherein the siRNA is introduced into the cell by contacting the cell with a composition comprising the siRNA and a lipophillic carrier.

43. The method of claim 40, wherein the siRNA is introduced into the cell by transfecting or infecting the cell with a vector comprising nucleic acid sequences capable of producing the siRNA when transcribed in the cell.

44. The method of claim 40, wherein the siRNA is introduced into the cell by injecting into the cell a vector comprising nucleic acid sequences capable of producing the siRNA when transcribed in the cell.

45. The method of claim 44, wherein the vector comprises transgene nucleic acid sequences.

46. The method of any one of claims 40-45, wherein the target mRNA specifies the amino acid sequence of a protein involved or predicted to be involved in a human disease or disorder.

47. A cell obtained by the method of any one of claims 40-46.

48. The cell of claim 47 which is of mammalian origin.

49. The cell of claim 47 which is of murine origin.

50. The cell of claim 47 which is of human origin.

51. The cell of claim 47, which is an embryonic stem cell.

52. An organism derived from the cell of claim 51.

53. A method of activating target-specific RNA interference (RNAi) in an organism comprising administering to said organism the siRNA of any one of the preeceeding claims, said siRNA being administered in an amount sufficient for degradation of the target mRNA to occur, thereby activating target-specific RNAi in the organism.

54. The method of claim 53, wherein the siRNA is administered by an intravenous or intraperitoneal route.

55. The method of claim 53, wherein the target mRNA specifies the amino acid sequence of a protein involved or predicted to be involved in a human disease or disorder.

56. An organism obtained by the method of any one of claims 53-55.

57. The organism of claim 56 which is of mammalian origin.

58. The organism of claim 56 which is of murine origin.

59. The organism of claim 56 which is of human origin.

60. The organism of any one of claims 56-59, wherein the target mRNA specifies the amino acid sequence of a protein involved or predicted to be involved in a human disease or disorder.

61. The organism of any one of claims 56-59, wherein degradation of the target mRNA produces a loss-of-function phenotype.

62. The method of claims 40-45 and 53-55, wherein degradation of the target mRNA is such that the protein specified by said target mRNA is decreased by at least 10%.

63. A method of treating a disease or disorder associated with the activity of a protein specified by a target mRNA in a subject, comprising administering to said subject the siRNA of any one of the preceeding claims, said siRNA being administered in an amount sufficient for degradation of the target mRNA to occur, thereby treating the disease or disorder associated with the protein.

64. A method for deriving information about the function of a gene in a cell or organism comprising:

(a) introducing into said cell or organism the siRNA of any one of the preceeding claims; and

(b) maintaining the cell or organism under conditions such that target-specific RNAi can occur;

(c) determining a characteristic or property of said cell or organism; and

(d) comparing said characteristic or property to a suitable control,

the comparison yielding information about the function of the gene.

65. A method of validating a candidate protein as a suitable target for drug discovery comprising:

(a) introducing into a cell or organism the siRNA of any one of the preceeding claims; and

(b) maintaining the cell or organism under conditions such that target-specific RNAi can occur;

(c) determining a characteristic or property of said cell or organism; and

(d) comparing said characteristic or property to a suitable control,

the comparison yielding information about whether the candidate protein is a suitable target for drug discovery.

66. A kit comprising reagents for activating target-specific RNA interference (RNAi) in a cell or organism, said kit comprising:

(a) the siRNA molecule of any one of the preceeding claims; and

(b) instructions for use.

67. A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), wherein the sense strand or antisense strand is modified by the substitution of at least one internal nucleotide with a modified nucleotide, and wherein the antisense strand is capable of adopting an A-form helix when in association with a target RNA.

68. A small interfering RNA (siRNA), comprising a sense strand and an antisense strand, wherein the antisense strand has a sequence sufficiently complementary to a target mRNA sequence to direct target-specific RNA interference (RNAi), wherein the sense strand or antisense strand is modified by the substitution of at least one internal nucleotide with a modified nucleotide, and wherein the antisense strand is capable of adopting an A-form helix having a normal major groove when in association with a target RNA.

69. An siRNA derivative comprising an siRNA having two complementary strands of nucleic acid, wherein the two strands are crosslinked, a 3' OH terminus of one of the strands is modified, or the two strands are crosslinked and modified at the 3'OH terminus.

70. The siRNA derivative of claim 69:

(a) wherein the siRNA contains a single crosslink.

(b) wherein the siRNA is psoralen crosslinked.

(c) comprising a biotin at a 3' terminus.

(d) comprising a photocleavable biotin having the structure depicted in Fig. 20 at a 3' terminus.

(e) comprising a peptide at a 3' terminus.

(f) comprising a nanoparticle, peptidomimetic, or dendrimer at a 3' terminus.

(g) comprising a Tat peptide at the 3' terminus.

71. A method of inhibiting expression of an RNA, the method comprising introducing into a cell the siRNA derivative of claim 69 or 70, wherein the siRNA derivative is targeted to the RNA.

72. A method comprising contacting a cell with a concentration of an siRNA derivative sufficient to inhibit expression of a target gene, wherein the siRNA derivative:

(a) is a crosslinked siRNA;

(b) contains a single crosslink;

(c) is psoralen crosslinked.

(d) is modified at a 3' terminus

(e) comprises a biotin at a 3' terminus.

(f) comprises a photocleavable biotin having the structure depicted in Fig. 8 at a 3' terminus.

(g) comprises a peptide, nanoparticle, peptidomimetic, or dendrimer at a 3' terminus.

(h) comprises a Tat peptide at a 3' terminus.

73. The method of claim 72, wherein the siRNA derivative inhibits expression of the target gene at least 30%.

74. The method of claim 72, wherein the cell is a mammalian cell.

75. The method of claim 72, wherein the cell is a human cell.

76. The method of claim 72, wherein the concentration of the siRNA derivative does not completely inhibit expression of the target gene.

77. The method of claim 72, wherein the contacting of the cell with the modified siRNA is carried out in the absence of a transfection reagent.

78. The method of claim 72, wherein the siRNA derivative comprises a Tat sequence at a 3' terminus.

79. A photocleavable biotin of the formula depicted in Fig. 20.

80. A method of determining whether a candidate siRNA derivative is an siRNA derivative, the method comprising

(a) obtaining a reporter cell comprising two different fluorescent reporter genes,

(b) transfecting the reporter cell with a candidate siRNA derivative targeted to one of the fluorescent reporter genes, thereby creating a test cell;

(c) incubating the test cell for a time sufficient for a reporter cell to express detectable levels of the fluorescent reporter proteins encoded by the fluorescent reporter genes;

(d) determining the fluorescence intensity of each fluorescent reporter protein in the test cell; and

(e) determining the ratio of the level of fluorescence intensity between the two fluorescent reporter proteins in the test cell and normalizing the ratio to the ratio of fluorescence intensity in a control reporter cell that was not transfected with the candidate siRNA derivative, wherein a normalized ratio of less than one indicates that the candidate siRNA derivative is an siRNA derivative.

81. The method of claim 80, wherein the control reporter cell is transfected with an antisense sequence that is complementary to the targeted reporter gene.

82. The method of claim 80, wherein the two reporter proteins are Green Fluorescent Protein (GFP) and Red Fluorescent Protein (RFP).

83. The method of claim 80, wherein the normalized ratio is at least 0.3.